
Laparoscopic Staging of Malignant Disease

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The earliest applications of laparoscopy were for diagnostic procedures. The goal was to make a diagnosis while sparing the patient a major, and often futile, operation. However, the view was limited and it was not possible to palpate organs or masses. The recent development of advanced laparoscopic techniques and ultrasound have improved our view and restored our "sense of touch". These innovations bring the goal of minimally invasive diagnosis and staging closer to reality. This paper reviews the current literature on the laparoscopic staging of cancer with an emphasis on patient selection, diagnostic accuracy, and the reduction in morbidity which can be achieved.

Introduction

Over the last decade therapeutic laparoscopy has undergone an explosive growth. Early success with laparoscopic cholecystectomy has encouraged innovative surgeons to apply minimal access techniques to a growing list of procedures. It has also led us to return to our historic roots. Before the advent of the CCD camera and the increasingly sophisticated instruments, laparoscopy was used primarily for diagnosis. Inspection of the viscera and biopsy of abnormal tissue were the primary goals.

Diagnostic laparoscopy was introduced by Ott, a Russian gynecologist, in 1903¹ and by Kelling.² A few years later, the concept of the pneumoperitoneum was formulated and the word "laparoscopy" coined by Jacobaeus.³ He also described the diagnosis of cirrhosis, metastatic disease, and tuberculous peritonitis. As part of the worldwide effort to "stage" malignant diseases, Benedict was among the first to discover that gastric, colonic, and ovarian malignancies could produce ascites.⁴

The development of a standardized system of staging malignant disease paralleled the progress in diagnostic laparoscopy. The early work of Pierre Denoit⁵ in the 1940s was formalized in the 1980s when the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) adopted the TNM (Tumor, Nodes, Metastases) system.⁶

Diagnostic laparoscopy can be complementary to other modalities and detect lesions beyond the resolution of other imaging methods. Its use to improve the staging and to allow the palliative treatment of advanced disease is becoming even more common.

Patient Selection and Techniques

Since general anesthesia and a pneumoperitoneum are generally required to optimize diagnostic laparoscopy, it is important to thoroughly evaluate the patient's cardiac and pulmonary system. In elderly patients with compromised function, monitoring end-tidal CO₂ will be necessary to prevent respiratory acidosis. The decreased venous return which a pneumoperitoneum and the reverse Trendelenberg position can produce makes the accurate assessment of intravascular volume critical. Sequential compression stockings, a Foley catheter, and a beanbag to support the patient during frequent position changes are even more important in this high-risk group.

Alternate access techniques may be necessary if the patient has had prior surgery or if there are masses or ascites present. The first step is a thorough inspection of the entire peritoneal cavity. This may detect small serosal implants which have eluded preoperative imaging. Relatively advanced laparoscopic skills are required. The surgeon must be comfortable entering the lesser sac or the retroperitoneum and obtaining tissue by biopsy or nodal dissection. Intraoperative ultrasound may compensate for the inability to palpate structures during laparoscopy. Collaboration with a trained ultrasonographer will make this a much more rewarding effort. Changing the patient's position will facilitate these procedures.

Staging Gastrointestinal Malignancies

There is ample evidence to suggest that the sensitivity and specificity of diagnostic laparoscopy can rival, and perhaps, surpass that of the usual preoperative imaging methods.⁷⁻¹¹ When coupled with intraoperative ultrasound, this advantage may even be greater. Since neither chemo nor radiation therapy can provide significant long-term survival for patients with extensive metastatic disease, avoiding unnecessary open explorations and permitting less morbid palliative procedures are important goals in the care of cancer patients. However, the procedure is not without risk. It should only be used in those cases where the potential diagnostic gain outweighs any risk.

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Tumors of the Esophagus and Cardia

The current staging of these tumors is aimed at assessing the depth of wall penetration, lymphatic spread, and systemic metastases.¹² If paraesophageal nodal disease is present, five-year survival for most patients with esophageal carcinomas is unlikely. Early detection and careful staging can minimize the frequency of futile resections while identifying those who might benefit from aggressive treatment. Only accurate tumor staging allows an adequate selection of appropriate treatment and a correct assessment of the response to preoperative therapy. Both endoscopic ultrasound and diagnostic laparoscopy can contribute to this precision. Stein, et al¹³ recently reported a prospective study of 127 patients with no evidence of metastatic disease referred for surgery or multimodal therapy. Diagnostic laparoscopy with peritoneal lavage was performed in each case. Because of technical problems with the probe, a complete laparoscopic ultrasound examination was completed in only 88 of the 127 patients. Forty-four relevant new findings were noted in 31 (24.4%) patients. Sixteen unsuspected liver metastases were found. Fourteen of these were only found by laparoscopic ultrasound. The sensitivity and specificity of laparoscopic ultrasound, percutaneous ultrasound, and CT in evaluating celiac axis lymph nodes are shown in Table 1.

Tumors of the Stomach

Although declining in incidence, gastric cancer remains a common problem. Since most patients present with advanced disease, it is still a major cause of cancer deaths. Resections for "cure" are undertaken in less than 60%. At celiotomy, more than 25% will be found to have been understaged by preoperative imaging.¹⁴ Since standard adjuvant chemotherapy has done little to improve survival, there is a growing interest in neo-adjuvant (treatment given prior to surgery) protocols for these patients. For this approach to be successful, the patients must be accurately staged prior to their treatment. Diagnostic laparoscopy might be very useful for those with apparently resectable disease.

In a recent series from Spain,¹⁵ 76 patients with presumably resectable cancers underwent diagnostic laparoscopy with intraoperative laparoscopic ultrasound. Thereafter, twenty-nine (40.8%) were found to be unresectable. The main reasons were peritoneal metastases in 16, malignant ascites in 15, liver metastases in 12, Krukenberg tumor in 2, and retroperitoneal fixation in 8. The other 42 patients were judged resectable. Only one of those was found to be unresectable at celiotomy. Consequently, the diagnostic accuracy of laparoscopy in determining resectability was 98.6% (70 of 71 patients). The sensitivity and specificity as confirmed by histology or celiotomy are shown in Table 2.

Results such as these have led to a wider application of diagnostic laparoscopy to select patients more precisely for neoadjuvant therapy and "curative" resection of gastric cancer.¹⁶

Pancreatobiliary Cancer

Primary pancreatobiliary carcinoma is an ideal opportunity for diagnostic laparoscopy. Despite the continuous development of noninvasive imaging techniques, a large number are found to have unsuspected metastatic disease at the time of exploration.¹⁷ Lavage studies indicate that as many as 40% of patients with pancreatic carcinoma already have diffuse peritoneal disease at the time of

Table 1. — The sensitivity and specificity of ultrasound and CT in evaluating nodes in the celiac plexus. Stein, 1997¹³

	Sensitivity ("True Positive")	Specificity ("True Negative")
Laparoscopic Ultrasound	67%	92%
Percutaneous Ultrasound	35%	78%
Computed Tomography	47%	82%

Table 2. — Multicenter comparison of video-laparoscopic staging of gastric cancer. Ascencio, 1997¹⁵

	Sensitivity ("True Positive")	Specificity ("True Negative")
Serosal infiltration	77%	100%
Lymph node metastases	62.5%	100%
Liver metastases	100%	100%
Peritoneal metastases	89%	100%
Retroperitoneal infiltration	57%	100%
Ascites	100%	100%

Table 3. — Laparoscopic staging of pancreatic cancer. Pietrabissa, 1996²³

Standard Imaging	Findings at Laparoscopy	Surgical Outcome
25 suspected pancreatic carcinomas - believed to be resectable	9 unresectable	3 pancreatectomies with vascular resection
	3 with locally advanced disease and/or portal vein encasement	
	2 change of diagnosis	10 standard pancreatic resections
	9 confined tumors	1 exploration alone

presentation.¹⁸ Early detection of disseminated disease may avoid unnecessary exploration in nearly a third of the patients sent for surgery¹⁹⁻²¹ and permit laparoscopic an/or endoscopic palliation.

Visual laparoscopy alone is inadequate to thoroughly evaluate the pancreas or the biliary tract for evidence of locally unresectable or distant disease. The addition of contact ultrasound has proven its worth in open surgery.²² The addition of biopsy guides to laparoscopic ultrasound probes will facilitate sampling from the pancreas and the retroperitoneum.

Pietrabissa, et al²³ recently published their experience with 25 patients with suspected pancreatic cancer referred for surgery. Preoperative staging to select those suitable for surgical referral was accomplished with ultrasound; dynamic, contrast enhanced CT; selective visceral angiography; and ERCP. Ascites or peritoneal washings were sent for cytology at the beginning of each case. Visual inspection of the peritoneum and liver followed. Attention was then turned to the ligament of Treitz and the base of the mesentery. Laparoscopic access to the lesser sac permitted direct



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The antimicrobial action may be attributable to inhibition of microbial cellular protein synthesis. A normalization of keratinization leading to an anticomedomal effect of azelaic acid may also contribute to its clinical activity. Electron microscopic and immunohistochemical evaluation of skin biopsies from human subjects treated with AZELEX[®] demonstrated a reduction in the thickness of the stratum corneum, a reduction in number and size of keratohyalin granules, and a reduction in the amount and distribution of filaggrin (a protein component of keratohyalin) in epidermal layers. This is suggestive of the ability to decrease microcomedo formation. **Pharmacokinetics:** Following a single application of AZELEX[®] to human skin *in vitro*, azelaic acid penetrates into the stratum corneum (approximately 3 to 5% of the applied dose) and other viable skin layers (up to 10% of the dose is found in the epidermis and dermis). Negligible cutaneous metabolism occurs after topical application. 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After topical treatment with AZELEX[®] in humans, plasma concentration and urinary excretion of azelaic acid are not significantly different from baseline levels. **INDICATIONS AND USAGE:** AZELEX[®] is indicated for the topical treatment of mild-to-moderate inflammatory acne vulgaris. **CONTRAINDICATIONS:** AZELEX[®] is contraindicated in individuals who have shown hypersensitivity to any of its components. **WARNINGS:** AZELEX[®] is for dermatologic use only and not for ophthalmic use. There have been isolated reports of hypopigmentation after use of azelaic acid. Since azelaic acid has not been well studied in patients with dark complexions, these patients should be monitored for early signs of hypopigmentation. **PRECAUTIONS:** General: If sensitivity or severe irritation develop with the use of AZELEX[®], treatment should be discontinued and appropriate therapy instituted. **Information for patients:** Patients should be told: 1. To use AZELEX[®] for the full prescribed treatment period. 2. To avoid the use of occlusive dressings or wrappings. 3. To keep AZELEX[®] away from the mouth, eyes and other mucous membranes. If it does come in contact with the eyes, they should wash their eyes with large amounts of water and consult a physician if eye irritation persists. 4. If they have dark complexions, to report abnormal changes in skin color to their physician. 5. Due in part to the low pH of azelaic acid, temporary skin irritation (pruritus, burning, or stinging) may occur when AZELEX[®] is applied to broken or inflamed skin, usually at the start of treatment. However, this irritation commonly subsides if treatment is continued. If it continues, AZELEX[®] should be applied only once-a-day, or the treatment should be stopped until these effects have subsided. If it troublesome irritation persists, use should be discontinued, and patients should consult their physician. (See ADVERSE REACTIONS.) **Carcinogenesis, mutagenesis, impairment of fertility:** Azelaic acid is a human dietary component of a simple molecular structure that does not suggest carcinogenic potential, and it does not belong to a class of drugs for which there is a concern about carcinogenicity. Therefore, animal studies to evaluate carcinogenic potential with AZELEX[®] Cream were not deemed necessary. In a battery of tests (Ames assay, HGPRT test in Chinese hamster ovary cells, human lymphocyte test, dominant lethal assay in mice), azelaic acid was found to be nonmutagenic. Animal studies have shown no adverse effects on fertility. **Pregnancy: Teratogenic Effects: Pregnancy Category B.** Embryotoxic effects were observed in Segment I and Segment II oral studies with rats receiving 2500 mg/kg/day of azelaic acid. Similar effects were observed in Segment II studies in rabbits given 150 to 500 mg/kg/day and in monkeys given 500 mg/kg/day. The doses at which these effects were noted were all within toxic dose ranges for the dams. No teratogenic effects were observed. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. **Nursing Mothers:** Equilibrium dialysis was used to assess human milk partitioning *in vitro*. At an azelaic acid concentration of 25 $\mu\text{g/mL}$, the milk/plasma distribution coefficient was 0.7 and the milk/buffer distribution was 1.0, indicating that passage of drug into maternal milk may occur. Since less than 4% of a topically applied dose is systemically absorbed, the uptake of azelaic acid into maternal milk is not expected to cause a significant change from baseline azelaic acid levels in the milk. However, caution should be exercised when AZELEX[®] is administered to a nursing mother. **Pediatric Use:** Safety and effectiveness in pediatric patients under 12 years of age have not been established. **ADVERSE REACTIONS:** During U.S. clinical trials with AZELEX[®], adverse reactions were generally mild and transient in nature. The most common adverse reactions occurring in approximately 1-5% of patients were pruritus, burning, stinging and tingling. Other adverse reactions such as erythema, dryness, rash, peeling, irritation, dermatitis, and contact dermatitis were reported in less than 1% of subjects. There is the potential for experiencing allergic reactions with use of AZELEX[®]. 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ultrasonic scanning of the pancreas. The laparoscopic ultrasound, preferably with color Doppler, was very sensitive at detecting vascular invasion behind the head of the pancreas. For those judged resectable, definitive pancreatic resection was scheduled for 3-4 days after the staging procedure. The impact of laparoscopic inspection and ultrasound staging on surgical strategy in this series of 25 patients is shown in Table 3.

From December 1992 to August 1994, 115 patients seen at the Memorial Sloan-Kettering Cancer Center in New York with radiologically resectable peripancreatic tumors underwent extensive laparoscopy before a planned curative resection. In this series Brennan, et al²⁴ examined the peritoneal cavity, liver, lesser sac, porta hepatis, duodenum, transverse mesocolon, and celiac and portal vessels. A complete examination was possible in 108 of the 115 patients. Sixty-seven were considered to have resectable disease, and 61 resections were performed (91% accurate). Laparoscopy failed to detect hepatic metastases in 5 patients and portal venous encasement in 1 patient. Laparoscopic ultrasound was not routinely used. In two of the patients believed to be resectable after standard laparoscopy, the addition of laparoscopic ultrasonography detected hepatic metastases. The authors acknowledge that more regular use of laparoscopic ultrasound might have increased the accuracy to nearly 100%. Forty-one patients in this series were found to be unresectable at laparoscopy and were spared open exploration. In a series of patients from the same institution undergoing open exploration from 1993 - 1992, 35% were found to be resectable. With the advent of laparoscopic staging in the later series, the rate of resection was increased to 76% ($p < 0.00001$).

Staging laparoscopy for presumed pancreatic malignancies should be confined to those cases where other, less-invasive modalities are negative or inconclusive. Used in this manner it can avoid unnecessary celiotomy in up to 42%.

Colorectal Cancer

Currently, there is no absolute indication for diagnostic laparoscopy in the evaluation of colorectal malignancies. However, when combined with laparoscopic ultrasound, the approach may compensate for the loss of palpation and permit a more thorough evaluation of the liver. Using laparoscopy as a means to a "second-look" may also play a greater role in the future. Nearly one half of all colorectal carcinomas will recur and most of those will do so within two

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years.²⁵ Combining CEA levels and scanning, CT, diagnostic laparoscopy, and intraoperative ultrasound those patients with an early, potentially resectable, recurrence may be more rapidly and successfully treated.

Prostatic and Ovarian Cancer

Early enthusiasm for laparoscopic staging of prostate cancer has not been supported by clinical trials. Consequently, it is seldom performed.

Laparoscopy can be helpful in staging GYN malignancies by providing periaortic node samples and facilitating "second look" operations. However, because the findings seldom materially affect the need for or extent of surgery, it is not frequently employed.

Diagnosis and Staging of Abdominal Lymphomas

With the exception of Hodgkin's Disease, the advent of high-quality imaging techniques has reduced the need for surgical staging of abdominal lymphomas. Although peripheral nodes may show the presence of lymphoma, abdominal exploration is still recommended for more than 85% of Hodgkin's patients.²⁶ 20-25% will be upstaged (more widespread disease) after abdominal exploration.²⁷ Biopsy of the liver and periaortic nodes and splenectomy can be accomplished with yields similar to open surgery with less operative morbidity. Whole node excision or wedge biopsy is used to prevent crush artifact. Advanced laparoscopic skills are essential to a thorough staging procedure.

Conclusion

Diagnostic laparoscopy utilizing ultrasonography can provide a major advantage in the accurate staging of intraabdominal malignancies. As neoadjuvant protocols are developed for some tumors, such precise staging will be critical to optimizing treatment choices and monitoring treatment response. Further clinical trials are necessary to determine whether the trauma-induced immunosuppression seen after celiotomy will be mitigated by a laparoscopic approach. The issue of port site recurrence has reduced the early enthusiasm for laparoscopic colectomies. A similar concern must be expressed about the use of laparoscopy for staging malignancies. Careful

attention to technique and surveillance will be critical to characterizing and minimizing this threat.

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